REMARKS

Claims 1, 4, 6-47, 49-53, and 55 are pending. Claims 10, 13-47, and 49-53 are withdrawn. Claims 2, 3, 5, 48, and 54 have been canceled. Claim 55 has been added. Claim 1 was amended to describe that at least one recombinant nucleic acid molecule comprising a reporter gene encoding a product that is secreted upon cell differentiation includes at least one cell type-specific promoter sequence operably linked to said reporter gene. Support for this amendment is found in the specification, *e.g.,* in page 9, lines 26-30. Claim 4 has been amended to delete the phrase "derived from". Claim 6 has been amended to delete reference to the promoter sequence, which was incorporated into independent claim 1. Claim 55 has been added and describes the determining step as including correlating the amount or activity of the secreted reporter gene product within a body fluid of said transgenic non-human animal or the cell culture medium of said cells with the amount of differentiated cells. Support for this is claim is found, *e.g.,* in page 20, lines 24-31. No new matter has been added by these amendments. Entry of this amendment is respectfully requested.

Applicants acknowledge with appreciation the withdrawal of claims 1-8 and 11 under 35 U.S.C. § 102(b), claims 1-9, 11 and 12 under 35 U.S.C. § 103(a), the Double Patenting Warning, the objection to specification, and the written description rejection under 35 U.S.C. §112.

Reconsideration of the remaining rejections is respectfully requested.

1. Finality of the Office Action Mailed March 30, 2011

At the outset, Applicants disagree that Applicants' amendments necessitated the new grounds of rejection presented in the Final Office Action mailed March 30, 2011. Applicants note that, in the Final Office Action, claims 1, 4, 6-9 and 11-12 were rejected under 35 U.S.C. §

102(b) as allegedly anticipated by Benkel *et al.* (WO 98/49320, "Benkel") and claims 1, 4, 6-9 and 11-12 were rejected under 35 U.S.C. §103 over Benkel et al. in view of Goldspink *et al.* and Bronstein *et al.* However, in the previous Office Action mailed October 13, 2010, claims 1-8 and 11 were rejected under 35 U.S.C. § 102(b) over Goldspink *et al.* and claims 1-9, 11 and 12 were rejected under 35 U.S.C. § 103 over Wobus in view of Benkel.

Applicants respectfully submit that the new anticipation rejection over Benkel *et al.* was not necessitated by the amendments of January 13, 2011. In the January 2011 response, the claims were amended to recite that the recombinant nucleic acid molecule (i) include "at least one cell-type specific regulatory sequence operably linked to said reporter gene," (ii) require that the "reporter gene product comprises a secretory leader sequence," and (iii) to state that "the secreted reporter gene product is not recaptured from said body fluid or cell culture medium." However, these claim amendments did not necessitate the new anticipation rejection over Benkel particularly since Benkel was relied upon by the Examiner in the first Office Action in the obviousness rejection. In fact, it appears that the teachings relied upon in the Benkel anticipation rejection (*e.g.*, "advantages of using a reporter gene product whose expression product is secretable for monitoring mammalian gene regulations [sic] (entire article; abstract)," Office Action mailed October 13, 2010 at p. 7) are the same teachings relied upon in the obviousness rejection of the October 13, 2010 Office Action. Accordingly, Applicants respectfully request withdrawal of the finality of the March 30, 2011 Office Action.

2. Claim Rejections – 35 U.S.C. § 112, Second Paragraph

The Office Action rejects claims 1, 4, 6-9 and 11-12 as allegedly being indefinite under 35 U.S.C. § 112, second paragraph. Claim 4 is rejected as allegedly being indefinite for the

recitation, "cells are derived from embryonic stem cells." Applicants respectfully traverse the rejection.

The rejection states that "[a]ll cells in an organism are derived from embryonic stem cells and hence it duplicates claim 1." Applicants have deleted the language "derived from" in claim 1. Applicants believe that these amendments obviate the instant rejection and request withdrawal thereof.

3. Claim Rejections – 35 U.S.C. § 112, First Paragraph

The Office Action rejects claims 1, 4, 6-9 and 11-12 under 35 U.S.C. §112, first paragraph, as the specification allegedly is not enabled "for any construct of reporter gene without an operatively linked promoter." The Examiner notes that the specification is

> . . . enabled for a method of monitoring differentiation of stem cell into specific cell lineage by measuring the amount of secreted activity of a reporter gene product by the differentiated cell wherein said gene expressed in the differentiating cell under the control of an operatively linked to a promoter. (Office Action at p. 4)

Applicants respectfully traverse the rejection. However, in the interest of expediting the prosecution of this application and without acquiescing to the rejection, Applicants have amended independent claim 1 to recite that a cell-type specific promoter is operably linked to the reporter gene. Withdrawal of the rejection is respectfully requested.

4. Claim Rejections – 35 U.S.C. § 102

Claims 1, 4, 6-9 and 11-12 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Benkel.

The rejection states that Benkel "teaches the advantages of using a reporter gene system for studying the regulation of gene expression that is of fundamental importance among others to cell division and cell differentiation." Applicants respectfully disagree with the characterization of the Benkel reference.

To anticipate claimed subject matter, a reference must disclose *each and every element* of the claimed invention, whether it does so explicitly or inherently. *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 471 F.3d 1369, 1375 (Fed. Cir. 2006). The elements must be "arranged or combined in the same way as in the claim," *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1370 (Fed. Cir. 2008). The reference must also "enable one of ordinary skill in the art to make the invention without undue experimentation." *Impax Labs., Inc. v. Aventis Pharms. Inc.*, 545 F.3d 1312, 1314 (Fed. Cir. 2008); see *In re LeGrice*, 301 F.2d 929, 940–944 (C.C.P.A. 1962).

The claims are directed to a method for *monitoring cell differentiation* comprising cells capable of differentiation. According to the method, these cells contain at least one recombinant nucleic acid molecule comprising a reporter gene encoding a product that is secreted upon cell differentiation and at least one cell type-specific promoter sequence operably linked to said reporter gene, or maintaining a non-human animal comprising said cells, under conditions allowing differentiation of said cells. The claim further requires that the amount or activity of the reporter gene product within a body fluid of said transgenic non-human animal or the cell culture medium of said cells is determined, wherein the reporter gene product comprises a secretory leader sequence, and wherein the secreted reporter gene product is not recaptured from said body fluid or cell culture medium.

Applicants respectfully note that the Benkel application describes a "secreted reporter gene system based on one or more alpha-amylases, which are elecrophoretically distinct variants of each other, for simultaneous expression in mammalian cells." (Benkel, p. 1, ll 3-6.) It does *not* describe a method of monitoring cell differentiation. At most, the Benkel application has a single statement in the abstract about cell differentiation: "The regulation of gene expression is of fundamental importance to all biological functions including adaptation to environmental conditions, cell division and differentiation, and the development of disease states such as cancer." (Abstract.)

However, Benkel utterly fails to imply – let alone enable the skilled artisan – how its method could be applied to *distinguish between differentiated and undifferentiated* cell lines. Rather, its focus is on distinguishing between *transformed mammalian cells versus untransformed mammalian* cells through the electrophoretic detection of secreted α-amylases. In fact, each of the cell lines transformed in the Benkel application is *already differentiated.*

The present invention, on the other hand, is directed to distinguishing between *differentiated versus undifferentiated* cells by the detection of differentiation-dependent secreted reporter gene products. Nothing in Benkel teaches, suggests or enables this method as claimed.

Therefore, Benkel does not anticipate claim 1 because, *inter alia*, it does not teach and enable a method of monitoring cell differentiation utilizing cells capable of differentiating. *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 471 F.3d 1369, 1375; *Impax Labs., Inc. v. Aventis Pharms. Inc.*, 545 F.3d 1312, 1314.

Accordingly, the anticipation rejection is improper and withdrawal thereof is respectfully requested.

5. Claim Rejections – 35 U.S.C. § 103

The Office Action rejects claims 1, 4, 6-9 and 11-12 under 35 U.S.C. §103(a) as, allegedly, being unpatentable over Benkel *et al.* (WO 98/49320) in view of Goldspink *et al.* (US 2003/0008836; "Goldspink") and Bronstein *et al.* (1994, *Biotechniques* 17:172-177; "Bronstein").

Benkel is asserted to teach the "advantages of using a reporter gene system for studying the regulation of gene expression that is of fundamental importance among others to cell division and cell differentiation" as well as to describe "reporter genes whose expression is secretable for monitoring the same." Final Office Action of March 30, 2011 at p. 6

Goldspink is relied upon to teach a "method of detecting myoblast differentiation by transfecting recombinant nucleic acid molecules encoding a human alpha-gal reporter gene under the control of promoter comprising MLC1/3 enhancer to undifferentiated myoblasts wherein the reporter gene was expressed and secreted from differentiated muscle cell in vitro culture." Final Office Action of March 30, 2011 at p. 6

Finally, Bornstein is relied upon to teach "improvements in the detection sensitivity of SEAP reporter using chemiluminiscent assays of the secreted reporter from cells in culture or tissue [*sic*]." Final Office Action of March 30, 2011 at p. 6

The rejection states that "it would have been obvious for one of ordinary skill in the art to incorporate SEAP reporter gene of Benkel for *lacZ* gene in the reporter construct of Goldspink and follow the differentiation of stem cells to specific tissue types or cell types using [very] sensitive SEAP assays taught by Bornstein." Final Office Action at p. 7

The rejection asserts that one of ordinary skill would be motivated to use an "assayable secreted reporter that will not be captured by tissues or the cells for monitoring a gene regulation

during differentiation of a cell into tissue cell type as it is less invasive and avoids lysis of the cells." *Id.* Finally, the rejection states that there would have been a "reasonable expectation of success making and using recombinant progenitor or stem cell having a reporter gene construct that codes for a secretable reporter protein for evaluating and identifying the differentiated cells as the art teaches that it is routine to use a recombinant secretable reporter for marking differentiation." *Id.*

First, Benkel does *not* teach a method of monitoring cell *differentiation.* While it generically notes that the "regulation of gene expression is of fundamental importance to all biological functions including . . . cell division and differentiation," it is completely silent as to any steps needed to monitor cell differentiation. In fact, the Benkel application is completely silent as to the use of the alpha-amylase reporter genes as a differentiation-dependent reporter at all. In fact, it only utilizes differentiated cells and the alpha-amylase reporter gene and uses the reporter to differentiate between transformed cells and untransformed cells.

Moreover, Benkel teaches away from the use of SEAP as a reporter asserting that it is associated with "background activity problems." Benkel at p. 2, line 16. Benkel states that "chicken a-amylase is superior to SEAP as a secreted reporter enzyme in biological fluids such as cow's milk." Benkel at 26, line 14. It is improper to combine references in the context of a § 103 rejection, where the references teach away from their combination. *In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983); MPEP 2145

Second, Goldspink does not remedy the deficiencies of Benkel. Goldspink allegedly describes transfecting recombinant nucleic acid molecules encoding a human alpha-gal reporter gene under the control of promoter comprising MLC1/3 enhancer to undifferentiated myoblasts, wherein the reporter gene was expressed and secreted from differentiated muscle cell in vitro

culture. According to Goldspink, the secreted human alpha-gal is recaptured from the tissue culture medium. *See* Goldspink, para. 3. Therefore, while the reporter gene disclosed in Goldspink may be differentiation-dependent, it *must* be recaptured in order to be detected. The claims, on the other hand, require that the secreted gene product not be recaptured. As such, Goldspink also teaches away from the claimed methods which specifically disclaim recapturing the secreted reporter gene product from the body fluid or cell culture medium. *In re Grasselli*, 713 F.2d 731, 743.

Third, while Bornstein is cited to teach improvements in the sensitivity of SEAP reporters using chemiluminescent assays of the secreted reporter products from cells in culture or tissue, it does not give rise to a reasonable expectation that such reporter genes would be useful in differentiation-dependent systems in cells capable of *differentiating*. Bornstein and Benkel both report on the use of SEAP reporter genes to detect secreted gene products from transformed mammalian cells and Benkel specifically indicates that SEAP is associated with background problems.

Neither of these reference individually, or in combination, teach or suggest to one having ordinary skill in the art that the SEAP reporter gene can (1) be useful in constructs to transform cells capable of differentiating, (2) that such constructs would be activated upon the differentiation of a transformed cell capable of differentiating; or (3) that the gene product would be secreted upon the differentiation of the cell. Therefore, while Bornstein is potentially instructive on the usefulness of SEAP reporters to detect secreted reporter gene products in general, it does not lead one skilled in the art to reasonably expect that such system could be differentiation-dependent, as claimed herein.

The Federal Circuit has held that "[o]bviousness does not require absolute predictability of success . . . all that is required is a reasonable expectation of success." In re Kubin, 2008-1184, (Fed. Cir. 2009) citing In re O'Farrell, 853 F.2d 894, 903 (Fed. Cir. 1988). As such, even though an invention may be "obvious to try," it nevertheless remains patentable if the cited prior art combination fails to provide one of skill in the art (at the time of filing of the relevant application) with "a reasonable expectation of success."

In sum, Applicants respectfully submit that the rejection is improper for failing to render obvious the claimed invention. Withdrawal of the rejection is respectfully requested.

6. New Claim 55 is Allowable over Prior Art

Dependent claim 55 has been added and provides that the determining step includes correlating the amount or activity of the secreted reporter gene product within a body fluid of said transgenic non-human animal or the cell culture medium of said cells with the amount of cells that differentiated. Applicants respectfully submit that this claim is supported by the specification, for example, at page 20, lines 24-31, and is not taught or suggested by the prior art for the reasons set forth above. Furthermore, Applicants submit that the cited prior art further does not teach a method for monitoring cell differentiation, wherein the amount of secreted reporter gene products in the body fluid of said transgenic non-human animal or the cell culture medium of said cells is correlated to the amount of cells that differentiated. Accordingly, this new claim is allowable over the prior art.

Conclusion

In view of the foregoing amendments and remarks, Applicant respectfully requests reconsideration and reexamination of this application and the timely allowance of the pending claims. The Examiner is invited to telephone the undersigned if that would be helpful to resolving any issues.

It is believed that no fees are due; however, the commissioner is authorized to charge any fees and credit any overpayments to Deposit Account No. 50-5071. Additionally, please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 50-5071.

Respectfully submitted,

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